AD-A141 738 TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENTS OF AI3-3..(U) ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GROUND MD J V WADE ET AL. 1/1

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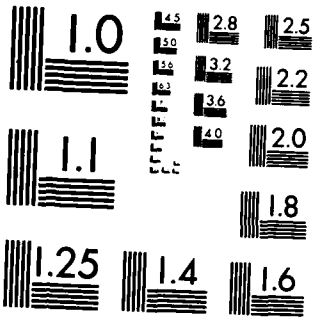

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UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010

TOPICAL HAZARD EVALUATION PROGRAM
OF
CANDIDATE INSECT REPELLENTS AI3-38359a, AI3-38282,
AI3-38277a, AI3-38865a, and AI3-38866a
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS
STUDY NOS. 75-51-0375-84, 75-51-0423-84,
75-51-0440-84, 75-51-0446-84, and 75-51-0447-84
APRIL 1982 - MARCH 1984

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REPORT DOCUMENTATION PAGE	READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER 75-51-0375, 0423, 0440, 0446, 0447-84 2. GOVT ACCESSION NO. AD-A141738	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Topical Hazard Evaluation Program of Candidate Insect Repellents AI3-38359a, AI3-38282, AI3-38277a, AI3-38865a, and AI3-38866a, US Department of Agriculture Proprietary Chemicals, Study No. 75-51-0375-84, 75-51-0423-84, 75-51-0440-84, 75-51-0446-84, 75-51-0447-84, Apr 82 - Mar 84	5. TYPE OF REPORT & PERIOD COVERED Final, April 1982 - March 1984 6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) John V. Wade, DVM, CPT(P), VC John G. Harvey, Jr.	8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS Commander US Army Environmental Hygiene Agency Aberdeen Proving Ground, MD 21010	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS Commander US Army Health Services Command Ft Sam Houston, TX 78234	12. REPORT DATE April 1982 - March 1984 13. NUMBER OF PAGES 8
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)	15. SECURITY CLASS. (of this report) Unclassified 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)
Approved for public release; distribution unlimited.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

USDA Proprietary Chemicals	AI3-38866a	Guinea Pig Sensitization
AI3-38359a	Skin Irritation	Topical Hazard Evaluation
AI3-38282	Eye Irritation	Program
AI3-38277a	ALD	
AI3-38865a	Photochemical Irritation	

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)
These compounds produced no primary irritation of the intact skin and no greater than mild primary irritation of the skin surrounding an abrasion. Chemicals AI3-38359a and AI3-38866a produced mild injury to the cornea and, in addition, some injury to the conjunctiva. Chemicals AI3-38277a, AI3-38865a, and AI3-38866a produced moderate injury to the cornea and, in addition, some injury to the conjunctiva. This injury had healed by 7 days post-application. Chemicals AI3-38859a and AI3-38282 produced moderate to marked sensitization in five of ten, and four of ten, guinea pigs, respectively. The other chemicals did not produce

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20. sensitization reactions. All tested chemicals did not cause a photochemical irritation reaction and demonstrated slight to moderate oral toxicity.

DEPARTMENT OF THE ARMY
U.S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

CPT(P) Wade/orl/AUTOVON
584-3980

REPLY TO ATTENTION OF

HSHB-OT/WP

1984

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents AI3-38359a, AI3-38282, AI3-38277a, AI3-38865a, and AI3-38866a, US Department of Agriculture Proprietary Chemicals, Study Nos. 75-51-0375-84, 75-51-0423-84, 75-51-0440-84, 75-51-0446-84, and 75-51-0447-84, April 1982 - March 1984

Executive Secretary
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20307

EXECUTIVE SUMMARY

The purpose, essential findings, and major recommendations of the inclosed report follow:

a. Purpose. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellents AI3-38359a, AI3-38282, AI3-38277a, AI3-38865a, and AI3-38866a by means of laboratory animal studies using New Zealand White rabbits, Sprague-Dawley rats, and albino Hartley guinea pigs.

b. Essential Findings. These compounds produced no primary irritation of the intact skin and no greater than mild primary irritation of the skin surrounding an abrasion. Chemicals AI3-38359a and AI3-38866a produced mild injury to the cornea and, in addition, some injury to the conjunctiva. Chemicals AI3-38277a, AI3-38865a, and AI3-38282a produced moderate injury to the cornea and, in addition, some injury to the conjunctiva. This injury had healed by 7 days post-application. Chemicals AI3-38359a and AI3-38282 produced moderate to marked sensitization in 5 of 10 and 4 of 10 guinea pigs tested, respectively. The other chemicals did not produce sensitization reactions. All tested chemicals did not cause a photochemical irritation reaction and demonstrated slight to moderate oral toxicity.

c. Major Recommendations. Recommend that chemical AI3-38866a be approved for further testing as a candidate insect repellent. Further testing should be conducted on chemicals AI3-38277a, and AI3-38865a only if their entomological efficacy is equivalent or superior to currently approved repellents due to their potential to produce occular injury. Recommend that chemicals AI3-38359a and AI3-38282 be disapproved for further testing due to their sensitizing potential.

FOR THE COMMANDER:

1 Incl
as (5 cy)

JOEL C. GAYDOS, M.D.
Colonel, MC
Director, Occupational and
Environmental Health

CF:
HQDA (DASG-PSP) wo incl
Cdr, HSC (HSCL-P)
Comdt, AHS (HSHA-P)
Dir, Advisory Cen on Tox, NRC (2 cy)
USDA, ARS (Dr. Terrence McGovern)
USDA, ARS-Southern Region (3 cy)
Cdr, USAMRDC [SGRD-DPM/LTC(P) Reinert]

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

REPLY TO ATTENTION OF

HSHB-OT/WP

TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENTS AI3-38359a, AI3-38282, AI3-38277a, AI3-38865a, and AI3-38866a US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS STUDY NOS. 75-51-0375-84, 75-51-0423-84, 75-51-0440-84, 75-51-0446-84, and 75-51-0447-84 APRIL 1982 - MARCH 1984

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research, Southern Region, Insects Affecting Man and Animals Research Laboratory, Gainesville, Florida, 29 April 1982.

b. Letter, US Department of Agriculture - Agricultural Research, Southern Region, Insects Affecting Man and Animals Research Laboratory, Gainesville, Florida, 10 February 1983.

c. Letter, US Department of Agriculture - Agricultural Research, Southern Region, Insects Affecting Man and Animals Research Laboratory, Gainesville, Florida, 2 June 1983.

d. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of the Army, Office of The Surgeon General; the Armed Forces Pest Control Board; and the Department of Agriculture, Agriculture Research, Science and Education Administrations; titled Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCE. Toxicology Division Topical Hazard Evaluation Program Procedural Guide, US Army Environmental Hygiene Agency (USAEHA), January 1982.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellents AI3-38359a, AI3-38282, AI3-38277a, AI3-38865a, and AI3-38866a, US Department of Agriculture (USDA) Proprietary Chemicals.

4. SUMMARY OF FINDINGS. Hazard evaluations of the candidate insect repellents AI3-38359a, AI3-38282, AI3-38277a, AI3-38865a, and AI3-38866a, USDA Proprietary Chemicals, were conducted by this Agency using New Zealand

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White rabbits, Sprague-Dawley rats, and albino Hartley guinea pigs. A tabular presentation of animal toxicity data developed by this Agency follows:*†

TABLE. PRESENTATION OF DATA

Test	Results	Interpretation
SKIN IRRITATION STUDIES		
Rabbits		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits. 0.5 mL technical grade chemical applied to each of six rabbits.	All tested chemicals did not produce primary irritation of the intact skin and no greater than mild primary irritation of the skin surrounding an abrasion.	USAEHA Category I (ref Appendix A)
EYE IRRITATION STUDIES		
Rabbits		
Single 24-hour application of 0.1 mL technical grade chemical to one eye of each of nine New Zealand White rabbits. Three of the nine rabbits had the eye flushed with warm water for 1 minute, 25 seconds after application.	Chemical AI3-38359a and AI3-38866a produced mild injury to the cornea and, in addition, some injury to the conjunctiva.	USAEHA Category C (ref Appendix A)
	Chemicals AI3-38282, AI3-38277a, and AI3-38865a produced moderate injury to the cornea and, in addition, some injury to the conjunctiva. Ocular injury had healed by 7 days post-application. Washing did not significantly decrease ocular injury.	USAEHA Category E (ref Appendix A)

* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education, and Welfare; National Institutes of Health (NIH) Publication No. 80-23, revised 1978, reprinted April 1980.
† The studies reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

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Test	Results	Interpretation
APPROXIMATE LETHAL DOSE		
Oral		
Rats (male) - no diluent	AI3-38359a >3,333 mg/kg AI3-38866a >5,000 mg/kg AI3-38282 987 mg/kg AI3-38277a 2,222 mg/kg AI3-38865a 987 mg/kg AI3-38866a >1,480 mg/kg	These chemicals demonstrated slight to moderate toxicity upon ingestion.
PHOTOCHEMICAL SKIN IRRITATION STUDIES		
Rabbits		
A single 0.05 mL application of a 25% (w/v) solution of each chemical and of a 10% (w/v) Oil of Bergamot solution (positive control) in 95% ethyl alcohol was applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to ultraviolet (UV) light (365 nm) for 30 minutes at a distance of 10-15 cm.	These chemicals did not produce photochemical irritation under test conditions.	These chemicals are not expected to produce a photochemical irritation reaction in humans.
Control		
Following UV exposure of the rabbits, 0.05 mL of test chemical, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for skin irritation at 24, 48 and 72 hours.	Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas.	

Study Nos. 75-51-0375-84, 75-51-0423-84, 75-51-0440-84, 75-51-0446-84, and 75-51-0447-84, Apr 82 - Mar 84

Test	Results	Interpretation
SENSITIZATION STUDIES Guinea Pigs (Female)		
Intradermal (ID) injections of 0.1 mL of a minimally irritating concentration of each tested chemical or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline:		
Ten test guinea pigs for each chemical were given 10 sensitizing doses over a 3-week period. After a 2-week rest, they were challenged with ID injections of each test chemical.	Challenge doses of AI3-38277a, AI3-38865A, and AI3-38866a did not produce sensitization reactions.	These chemicals are not expected to produce a sensitization reaction in humans.
	Chemicals AI3-38359a and AI3-38282 produced moderate to marked sensitization reactions in 5 of 10 and 4 of 10 guinea pigs, respectively.	These chemicals could produce sensitization reactions in humans.
Control		
Ten positive control guinea pigs were sensitized over 3-weeks with DNCB. After a 2-week rest, they were challenged with ID injections of DNCB.	Challenge dose of DNCB in positive control guinea pigs produced a marked sensitization reaction in 10 out of 10 guinea pigs.	These guinea pigs responded to sensitizing agents

* A known skin sensitizer.

5. CONCLUSION. These compounds produced no primary irritation of the intact skin and no greater than mild primary irritation of the skin surrounding an abrasion. Chemicals AI3-38359a and AI3-38866a produced mild injury to the cornea and, in addition, some injury to the conjunctiva. Chemicals AI3-38277a, AI3-38865a, and AI3-38282a produced moderate injury to the cornea and, in addition, some injury to the conjunctiva. This

injury had healed by 7 days post-application. Chemicals AI3-38359a and AI3-38282 produced moderate to marked sensitization in 5 of 10, and 4 of 10, guinea pigs, respectively. The other chemicals did not produce sensitization reactions. All tested chemicals did not cause a photochemical irritation reaction and demonstrated slight to moderate oral toxicity. These studies were monitored by the Analytical Quality Assurance Office (see Appendix B).

6. RECOMMENDATION. Recommend that chemical AI3-38866a be approved for further testing as a candidate insect repellent. Further testing should be conducted on chemicals AI3-38277a and AI3-38865a only if their entomological efficacy is equivalent or superior to currently approved repellents due to their potential to produce occular injury. Recommend that chemicals AI3-38359a and AI3-38282 be disapproved for further testing due to their sensitizing potential.

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APPROVED:

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Chief, Toxicology Division

APPENDIX A

TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation, and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.

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APPENDIX B

ANALYTICAL QUALITY ASSURANCE

The Analytical Quality Assurance Office certifies the following:

a. These studies were conducted in accordance with:

(1) Standing Operating Procedures developed by the Toxicology Division, USAEHA.

(2) Title 21, Code of Federal Regulations (CFR), 1983 rev, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

(3) Final Rule, Pesticide Programs; Good Laboratory Practice Standards; 48 Federal Register (FR) 53963-53969 , 29 November 1983.

b. Facilities were inspected during its operational phase to ensure compliance with paragraph a above.

c. The information presented in this report accurately reflects the raw data generated during the course of conducting these studies.

PAUL V. SNEERINGER, Ph.D.
Chief, Analytical Quality
Assurance Office

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